REMARKS/ARGUMENTS

Claims 1, 2, 4-8, 13, 15-16 and 20-45 were pending in the current application. Claims 1, 2, 4-8, 13, 15-16 and 20-45 have been rejected. Claims 23-26, 31-34, 39-42 and 44 are canceled herein without prejudice or disclaimer. Claim 35 has been withdrawn from consideration by the Examiner. Thus, claims 1, 2, 4-8, 13, 15, 16, 20-22, 27-30, 35-38, 43 and 45 are now pending.

Claims 1-2, 5-6, 13, 15-16, 20, 28-30 and 45 are amended herein. These amendments are supported by the Specification, drawings and claims as originally filed; no new matter has been added.

In regard to withdrawn claim 35, Applicants respectfully point out that per M.P.E.P. 809 02(a), if generic claims 5 is found to be allowable, then examination of all non-elected species claims including claim 35 will be necessary.

REJECTION UNDER 35 U.S.C. § 112, 2ND ¶

Claims 1, 4-8, 13, 15 and 16 were rejected under 35 U.S.C. §112, second paragraph as allegedly failing to set forth the subject matter which applicants regard as their invention. (See 4/13/05 Office Action, at page 3). The Examiner appears to have some confusion between SEQ ID NO: 61 and 63. In particular, the Examiner contends that there is an inconsistency in that in the amendment filed on January 29, 2004 SEQ ID NO: 63 is limited to 4 amino acids but in the sequence listing filed on September 20, 2004 is limited to 10 amino acids. However, Applicants believe that the issue is resolved by the fact that Applicants amended the Specification on February 20, 2004 to now indicate that SEQ ID NO: 63 is indeed limited to ten amino acids (See 02/20/04 Amendment, at page 2 which amended the paragraph beginning at page 9, line 2) and replaced SEQ ID NO:67 for [[SEQ ID NO: 63]] as the sequence that is limited to four amino acids (See 02/20/04 Amendment, at page 3 which amended the paragraph beginning at page 10, line 9). Accordingly, Applicants submit that the rejection is now moot in light of these prior amendments and therefore, respectfully request withdrawal of the rejection.

WRITTEN DESCRIPTION REJECTIONS UNDER 35 U.S.C. § 112, 1ST ¶ OF CLAIMS 20-22, 28-34 AND 36-38

Claims 20-22, 28-30 and 36-38 were rejected under 35 U.S.C. § 112, first paragraph for allegedly being directed to new matter. Applicants traverse this rejection. Specific support for the sequences (e.g., SEQ ID NO's: 100 -102) is found in the Specification, e.g., at page 9, lines 30-36, (e.g., SEQ ID NO's: 100 and 101) and page 10, lines 9-14 and 23-30 (e.g., SEQ ID NO: 102). With respect to "Formula IV", without acquiescing to the propriety of the rejection, and solely for purpose of expediting prosecution, Applicants have amended claims 20, 28 and 36 to obviate the rejection.

Claims 31-34 were rejected under 35 U.S.C. § 112, first paragraph. Applicants traverse this rejection. However, without acquiescing to the propriety of the rejections, and solely for purpose of expediting prosecution, Applicants have cancelled the claims thus mooting the rejection. Claim 5 has also been amended to now recite "wherein the DNA comprises a mutant sequence of SEQ ID NO: 4. Support for this amendment is found in the Specification at e.g., page 13, lines 16-20.

ENABLEMENT REJECTIONS UNDER 35 U.S.C. § 112, 1ST ¶ 0F CLAIMS 2, 4-8 AND 13, 15-16, 23-27, 31-34 AND 39-45

Claims 2, 4-8 and 13, 15-16, 23-27, 31-34 and 39-45 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the claims fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph. (See 4/13/05 Office Action, at page 4). Specifically, the Examiner has contended that the Specification does not provide any guidance on how to make polypeptides which meet all the structural limitations encompassed by claims and suppress neuronal cell death associated with Alzheimer's disease. (See 4/13/05 Office Action, at page 5). The Examiner further contends that one skilled in art will allegedly appreciate a polypeptide wherein one to five amino acids have been substituted, deleted, inserted and/or added "to the given polypeptide of SEQ ID NO: 5 will lead to a completely altered

structure with no similarity to the original twenty four amino acid long polypeptide of SEQ ID NO:5." *Id.*

As an initial matter, in order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have amended claims 2, 5 and 6 to now recite that "one amino acid has been substituted, deleted, inserted, and/or added." This will result in sequence homology of greater than 95% to SEQ ID No:5. Also claims 23-26, 31-34, 39-42 and 44 have been cancelled without prejudice or disclaimer, thus mooting the rejection with respect to these claims.

Applicants respectfully traverse the above rejection as the Examiner premises her rejections on contentions which are untenable. First, the Examiner provides no evidence or sound scientific reasoning as to why the skilled artisan would reach the above conclusions. Second, they are factually incorrect. A polypeptide having up to five altered amino acids altered from the polypeptide of SEQ ID NO:5 will still have greater than 79% identity with the polypeptide of SEQ ID NO:5 and even greater similarity. Further, a polypeptide having one altered amino acid will have greater than 95% identity with SEQ ID NO: 5 and even greater similarity. Thus contrary to the Examiner's assertion, the claimed polypeptides clearly have similarity to the original twenty four amino acid long polypeptide of SEQ ID NO:5.

Also, contrary to the Examiner's assertion regarding guidance on how to make the claimed polypeptides, the Specification provides extensive teaching on how to make polypeptides of SEQ ID NO: 5 which suppress neuronal death associated with Alzheimer's disease wherein one or more amino acids have been substituted, deleted, inserted and/or added. See, for example, Example 6 of the Specification, which describes that a polypeptide in which the C-terminal KRRA has been replaced with AAAA (SEQ ID NO: 10) shows similar functional activity to the original polypeptide (See the Specification at pages 48 to 49). Also, Example 15 describes a variant of SEQ ID NO: 5 that shows an activity of suppressing neuronal death that is even more potent than SEQ ID NO: 5 (See the Specification e.g., at pages 59-60). Additionally, Example 13 demonstrates that seven amino acids can be deleted from SEQ ID NO: 5 without loss of function (SEQ ID NO: 21). Further, Figure 23 shows that ten positions of the amino acid sequence of HNG17, a variant consisting of 17 amino acids (SEQ ID NO: 24), can be substituted

without loss of function. Other examples in the Specification of variants of SEQ ID NO: 5 that suppress neuronal death include SEQ ID NOs: 8, 12, 13, 22, 23, 26 -29, 32, 33, 37, 40, 46, 48, 54, and 60. In fact, the Specification provides guidance on how to make and use at least 22 variants which of SEQ ID NO: 5which suppress neuronal death.

Applicants have also previously noted a paper by, Carocasole *et al.* (FASEB J., 2002, 16: 1331-133) which further substantiates the neural protective activity of variants of SEQ ID NO: 5. The authors report a rat homolog of the polypeptide of SEQ ID NO: 5 which has an amino acid sequence in which six amino acids in SEQ ID NO: 5 are substituted (Fig. 1A of Carocasole *et al.*). This polypeptide shows neuroprotective activity as the polypeptide of SEQ ID NO: 5 (Fig. 1B and C)).

Moreover, the Specification as filed describes techniques for making variants of the claimed polypeptides (See e.g., page 7, line 10 to page 11, line 1) as well as assays for determining the neural protective activity of those variants (See the Specification e.g., at page 11, line 2 to page 12, line 1; and Examples 1-15 where the Specification provides teaching on three separate assays, see discussion herein). Thus, given this disclosure, the skilled artisan would have been readily able to make and use polypeptide variants of the amino acid sequence of SEQ ID NO:5 which suppress neuronal death without undue experimentation using techniques described in the Specification and known in the art.

Specific support for variants of SEQ ID NO: 5 that suppress neuronal death associated with Alzheimer's disease wherein one to five amino acids have been substituted, deleted, inserted, and/or added may be found in the Specification at e.g., page 12, lines 10-21. Also, support for conservative substitutions may be found in the Specification e.g., at page 12, line 22 to page 13, line 8.

Applicants submit that further support for the allowability of the claims can be found in the Revised Interim Written Description Guidelines Training Materials. Applicants submit that instant claims 2, 5 and 6 and their respective dependant claims, are analogous to the exemplary claim of Example 14, (Product by Function) of those Guidelines. Like the exemplary claim, the genus of peptides recited in claims 2, 5 and 6 is a discrete, well-defined genus of peptides having greater than 95% homology to the disclosed species (e.g., SEQ ID No: 5 has 24 amino acids in

which no more than 1 amino acid can vary). Any species of the claim can be readily envisaged. Further, as discussed herein, the function of such peptides is well defined, suppressing neuronal death associated with Alzheimer's disease. Also just like the exemplary claim, Applicants have defined an assay for determining this function, (actually, three assay, see herein). Just like the analysis of Example 14 of the Training Materials, the "species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the a least 95% identical variants of SEQ ID NO: [5] ..which are capable of the specified ..activity." Therefore, just as "[o]ne of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus" so to would they conclude that applicant has taught how to make and use all the members of that genus.

In light of the extensive nature of the evidence presented, Applicants submit there is more than ample support in Specification for making and using polypeptides of SEQ ID NO: 5 that suppress neuronal death associated with Alzheimer's disease, wherein one amino acid has been substituted, deleted, inserted, and/or added. This is further substantiated by the Revised Interim Written Description Guidelines Training Materials. Accordingly, for this and all the reasons above, Applicants respectfully request withdrawal of the rejection.

ENABLEMENT REJECTIONS UNDER 35 U.S.C. § 112, 1ST ¶ 0F CLAIMS 13-16 AND 45

Claims 13, 15, 16 and 45 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the claims fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph. (See 4/13/05 Office Action, at page 8). The Examiner would appear to contend that the Specification does not provide sufficient teaching for the skilled artisan to use the claimed polypeptides and/or polynucleotides to treat Alzheimer's disease in a human because, *inter alia*, i) the disclosure in the specification and knowledge in the art does not provide enablement for use of the claimed compositions in successful gene therapy, ii) the neuroprotective effect of the claimed polypeptides shown in vitro cannot be extrapolated for in vivo treatment of

neurodegeneration, iii) one would not expect to treat Alzheimer's disease by lessening Aβ neurotoxicity; iv) there is no evidence or reasoning that the administration of the claimed polypeptides would prevent or treat any neurodegenerative condition including pathologies not associated with Aβ toxicity; and v) the Specification has not provided information on the route of administration of the claimed pharmaceutical composition which satisfies the skilled artisan. (See 4/13/05 Office Action, at pages 9-10). Applicants respectfully traverse this rejection. Each of the Examiner's contentions will be addressed in turn.

In regard to the first basis for the rejection, Applicants respectfully assert that the use of the claimed compounds comprising DNA for gene therapy is enabled. The Specification provides extensive teaching on the use of the claimed DNA for gene therapy, (See the Specification e.g., at page 18, line 17, to page 19, line 8). Also the Examiner has failed to provide any evidence or sound scientific reasoning as to why the claimed DNA could be used for successful gene therapy. However, without acquiescing to the propriety of the rejection, and solely for purposes of expediting prosecution, Applicants have amended claim 13 to now recite "a pharmaceutical composition comprising the polypeptide of any one of claims 1 to 2." Accordingly, this aspect of the rejection as applied to claims 13, 15 and 16 is now considered moot.

In regard to the use of in vitro data, the courts have ruled that in vitro data can be used to support enablement of pharmaceutical inventions. *Cross v.Izuka,* 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Moreover, a rigorous or exact correlation between in vitro and in vivo activity is not required where "the disclosure of the pharmaceutical activity if reasonably based on the probative evidence." *Id.* As is explained below, the probative evidence in this case including the Specification and scientific research papers more than satisfies this requirement. In particular, the work Tajima et al. demonstrate a significant correlation between the in vitro and in vivo activity of the claimed polypeptides.

The Specification establishes a correlation between the in vitro and in vivo activity of the claimed polypeptides. In particular, the Specification teaches that the claimed polypeptides produced a dramatic neuroprotective effect for primary neurons exposed to Aβ 1-43 peptide (See the Specification e.g., at page 52, line 11 to page 53, line 5). As is discussed below, the links

between Aβ and the pathological mechanisms of Alzheimer's disease are strongly established by the current scientific research and the Specification itself suggests such. (See the Specification e.g., at page 51, line 35 to page 52, line 2).

Importantly, the neuroprotective effect conferred by claimed polypeptides was selective, i.e., no such effect was produced when primary neurons were exposed to Etoposide, an anticancer agent and has been reported to induce cell death of primary cultured neurons (See the Specification at page 51, lines 21-29). Therefore, by conferring a selective in vitro neuroprotective effect against Aβ 1-43 (a compound strongly linked with the in vivo pathological mechanism of AD, see discussion herein), the claimed polypeptides would be reasonably expected to do so in vivo in a human, thus satisfying the enablement requirements of *Cross*. Further support for an expected in vivo effect is seen in the fact that the claimed polypeptides also produced a neuroprotective effect for cells expressing neurodegenerative disease-causing FAD (familial Alzheimer's disease) genes (See e.g., Examples 7-9 of the Specification).

In addition to the above support, the in vivo effects of the claimed polypeptides have actually proven by the work of Tajima et al. (Humanin derivative, S14G-HN, prevents amyloid-beta-induced memory impairment in mice. J Neurosci Res. 2005 Mar 1;79(5):714-23, copy enclosed). Tajima et al. used a rodent model wherein rats received intracerebroventricular (icv) injection of Aβ peptide. This model is accepted as being closely related to human Alzheimer disease in that icv injection of cytotoxic Aβ peptides has been shown to cause neural degeneration including amnesia in rodents and primates . (See Tajima et al., at 715; Loo et al., at 7951). Tajima et al. found that an icv injection of S14G-HN [the polypeptide of SEQ ID NO: 8] prevented Aβ -induced impairment of short-term and long term memory in vivo."(Tajima et al., at 722). Moreover anatomical/histo-chemical analysis showed that S14G-HN sustained the number of cholinergic neurons in the basal forebrain including medial septum and the striata against Aβ insult and prevented Aβ -induced deterioration of spatial working memory and latent learning." (*Id* at 721). Thus, Tajima et al. showed a direct link between the effect of the claimed polypeptides in preserving long term and short term memory against Aβ -induced deterioration and the cellular in vivo neuroprotective effect which was earlier shown in vitro. Importantly, Tajima et al. conclude that "S14G-HN has rescue activity against memory impairment caused by

Aβ -related insults in vivo by activating **the same intracellular neuroprotective machinery as elucidated previously in vitro.**" (Tajima et al., abstract, emphasis added). Clearly, Tajima et al. demonstrate a significant direct correlation between the in vitro and in vivo neuroprotective activity of the S14G-HN polypeptide. On this basis alone, Applicants request withdrawal of the in vitro/in vivo correlation component of the rejection.

Additional support of an in vivo therapeutic effect of the claimed polypeptides is evidenced by the papers of Hashimoto et al. (Proc Natl. Acad. Sci. U S A. 2001 May 22; 98 (11): 6336–634) and Mamiya et al. (British J. Pharmacol. 2001, 134: 1597-1599) both of which were previously submitted. Hashimoto et al. demonstrated that the claimed peptides confer a neuroprotective effect to cells expressing Alzheimer's disease-linked genes but not Huntington's disease or amyotrophic lateral sclerosis-linked genes. This result again suggests that the neuroprotective effect of the claimed peptides is highly specific and that they are likely to provide a therapeutic benefit.

Mamiya et al. report the in vivo effects of the polypeptide of SEQ ID NO: 8 (S14G substitution of SEQ ID NO: 5). This paper teaches that cholinergic neuronal systems play an important role in the cognitive deficits associated with neurodegenerative diseases including AD, and that scopolamine antagonizes a muscarinic acetylcholine receptor, thereby inducing impairment of learning and memory (See page 1598, right column, "Discussion"). Figure 1 and Table 1 of Mamiya et al. demonstrate that intracerebroventricular (icv) administration to mice of the polypeptide of SEQ ID NO: 8 exerts the anti-amnesic effects on learning and memory deficits induced by scopolamine. Thus, Mamiya et al. further provides evidence that polypeptides of the invention will have a neuroprotective effect in-vivo.

The Examiner has contended that skilled artisan would not expect to prevent or treat Alzheimer's disease by possibly interfering Aβ neuro-toxicity. Applicants submit there is compelling scientific evidence that reducing Aβ neuro-toxicity would indeed by an effective treatment for Alzheimer's disease. The links between beta amlyloid peptides (AβP) and Alzheimer's disease are strongly established. The current scientific view holds that Aβ "is the major constituent of senile plaque" and its accumulation in "**senile plaques is a principle event in the neuropathology of Alzheimer's disease**" and "**is considered a major cause of AD**

[Alzheimer's disease]." (Loo et al. (Proc Natl Acad Sci U S A. 1993 Sep 1;90(17):7951-5, 51; copy enclosed); Tajima et al., at 721; emphasis added). There are multiple lines of evidence substantiating this view. First, is the fact that the family of Aβ peptides is produced in the brain of Alzheimer's patients and, as described above, is a major component of the plaques. In particular, "AβP deposits are associated with both the presence of dystrophic neuritis (1, 2) and the neuronal loss of found in severely affected brains" of Alzheimer's patients. (Loo et al., at 7951). Second, Hashimoto, Loo and other researchers have conclusively shown that when added to neuronal cultures, Aβ peptides induces cell death ("aggregates of AβP induce neuronal dystrophic neural morphology and neuronal loss" Loo et al., at 7591). Third, intra-cerebral injection (icv) of Aβ peptides into animals induces neural degeneration in rats and primates (*Id*). and a single injection has been shown to produce amnesia in mice (Tajima et al., at 715). Therefore, based on this compelling body of scientific research, Applicants assert that the skilled artisan would absolutely expect a protective agent that blocks Aβ neuro-toxicity (e.g., the polypeptide of SEQ ID No: 5) to be an effective treatment for Alzheimer's disease.

Against this weight of scientific evidence that the claimed polypeptides would and in fact do have an *in vivo* effect, the Office Action provides no sound scientific reasoning or evidence as to why the claimed polypeptides would not. Instead, the Office Action merely contends that the Specification fails to provide evidence to demonstrate a direct link between the claimed polypeptides and the successful treatment of a disease (4/13/05 Office Action, at page 9), but nowhere does the Office Action provide scientific evidence, papers etc. to support this contention. Such contentions are not sufficient so sustain the instant rejection in that the courts have held "[m]ere denials and conclusory statements, however, are not sufficient to establish a genuine issue of material fact." (McElmurry Arkansas Power & Light Co., 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131. Fed. Cir. 1993).

In addition to the above evidentiary deficiency, the Office Actions attempts to set a standard for enablement which is contrary to the law by requiring Applicants to demonstrate a direct link between the claimed polypeptides and the successful treatment of a disease. *Id.* This requirement in effect, would require Applicants to conduct clinical trials. However, it is well established that Applicants are not required to perform clinical trials to demonstrate enablement.

For example, in *In re Brana,* the Federal Circuit reversed a rejection in which the Office alleged claims were not enabled because the application did not prove a claimed pharmaceutical compound was useful. *In re Brana*, 34 USPQ2d 1436, 1440 (Fed. Cir. 1995). As described herein while applicants have not conducted clinical trials, the Specification together with research of Tajima et al. and others provides compelling evidence that the claimed polypeptides have an in vivo neuro-protective effect and thus are enabled for the treatment of Alzheimer's and other neuro degenerative diseases.

The Office Actions also appears to be requiring Applicant's invention to reverse every possible pathological aspect of Alzheimer's diseases in order to be enabled (See Office Action, at pages 9-10) However, a standard of enablement that requires the claimed compositions to reverse every aspect of a disease is unduly high. Courts have routinely found that the mere identification of a pharmacological activity that is relevant to an asserted pharmacological use is itself "obviously beneficial to the public." Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980). It follows that that a composition is enabled if the specification in combination with knowledge in the art teaches how to achieve such a pharmacological activity. "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." In re Brana, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). Here, the Specification provides abundant evidence that the claimed polypeptides have pharmacological activity, e.g., a neuro-protective activity (See the Specification at e.g., at page 52, line 11 to page 53, line 5). Moreover, this activity has been corroborated in vitro by the work of Carocasole et al. and Hashimoto et al., in vivo by Tajima et al. Given this evidence, it is submitted that speculation that the claimed compositions may not cure every aspect of Alzheimer's disease is not detrimental to enablement.

In regard to the fourth basis for the rejection, Applicants describe above in detail how the claimed compositions can be used to treat neurodegenerative conditions associated with Aβ toxicity such as Alzheimer's disease. In regard to neurodegenerative conditions not associated with A β toxicity, contrary to the Examiner's assertion, the Specification does indeed provide teaching for treating such conditions. Specifically the Specification teaches protective effects of

the claimed polypeptides against cell death induced by a presenilin 1 mutation (M146L PS-1) or a presenilin 2 mutation (N141I PS-2) (See Specification, e.g., at page 30, lines 23-30 and Figure 10).

In regard to the final basis for the rejection, the Examiner has alleged that the teaching in the Specification on the multiple routes of pharmaceutical administration"can not satisfy a skilled practitioner" (4/13/05 Office Action, at page 10). As an initial matter, without acquiescing to the propriety of the rejection, and solely for purposes of expediting prosecution, Applicants have amended claim 45 to now recite "an acceptable carrier" "vs. "a pharmaceutically acceptable carrier" thus mooting this aspect of the rejection as applied to claim 45.

Initially, it is submitted that enablement of a pharmaceutical composition does not require teaching how to use the composition in a patient. A pharmacological activity is itself "obviously beneficial to the public." *Nelson.* For the reasons discussed above, it is sufficient that the specification, in combination with knowledge in the art, teach how to obtain a pharmacological activity from the composition. Nonetheless, contrary to the Examiner's final basis for rejection (e.g., alleged lack of teaching on administration etc.), the Specification provides extensive teaching on the route, duration and quantity of administration of the claimed polypeptides for use in a pharmaceutical composition. For example, at page 20, lines 1-30, the Specification provides teaching on the formulation, route and methods of administration of the claimed polypeptides. Further, at page 20 line 23 to page 21, line 12, the Specification provides teaching on the concentration and dosage of the claimed polypeptides in a pharmaceutical composition. Applicants respectfully submit that this is more than sufficient teaching of how to use the claimed pharmaceutical compositions.

In particular, the Examiner appears to premise her rejection on the contention that the specification has not provided support for oral administration (see 4/13/05 Office Action, at page 10). This basis for the rejection is in error for two reasons. First, there is no requirement in the law that an applicant provide disclosure on use of a particular type of administration to meet the enablement requirement. ("Nothing more than objective enablement is required." In re Marzocchi,) Otherwise, whole classes of pharmaceuticals would be considered not enabled e.g.

intravenous pharmaceuticals where an oral administration route was not disclosed. Also, Applicants have provided extensive disclosure for other administration methods such as intracerebroventricular injection (See the Specification, e.g., at page 20, lines 1-30) which were well known at the time of filing (See e.g., Haley TG, McCormick WG. 1957. Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. Br J Pharmacol 12:12–15, copy enclosed). This latter method was used by Tajima et al. who showed that intra-cerebroventricular injection of the claimed polypeptides suppressed neuronal death associated with Alzheimer's disease with dosages that corresponded to those described in the Specification. (See Tajima et al., e.g. at the Abstract; See also the Specification at, e.g., page 21, lines 1-11). Accordingly, on this additional basis, Applicants respectfully request withdrawal of the rejection.

The above facts notwithstanding, the Specification does indeed provide ample teaching of oral administration. In particular, the Specification provides teaching of "oral administration" (Specification e.g., at page 20, line 17) oral forms for administering the claimed polypeptide including "a tablet, capsule.. elixir, suspension, syrup" (Specification e.g., at page 20, lines 9-10), as well as describing doses and means for determining doses (See the Specification, at page 21, lines 1-10 and page 20, lines 26-30). Accordingly, on this additional basis Applicants respectfully request withdrawal of the rejection.

Applicants also traverse the rejection in that the office action appears to lack clarity on the test used by the Examiner to determine enablement. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. *United Stated v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). "Nothing more than objective enablement is required." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). It is therefore irrelevant whether the teaching of the claimed invention is provided through broad terminology, or illustrative examples including prophetic examples. *Id*; See Also MPEP 2164.08(b), A*tlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)) ("prophetic examples do not make the disclosure nonenabling"). Importantly, as long as one method one is disclosed for making and using the claimed invention which enables the claim that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement

of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), cert. denied, 484 U.S. 954 (1987).

Given the extensive teaching in the Specification on the formulation, route and methods of administration of the claimed polypeptides (see above), Applicants assert that claims 13, 15 16 and 45 are more than enabled under the rule from *Telectronics*. Further, under the holdings from *In re Marzocchi* and *Spectra-Physics* the enablement requirement is met with regard to pharmaceutical administration if the specification provides teaching of only one form of administration. Applicants have more than met this requirement in that the Specification provides disclosure on use of multiple types of administration methods. (See the Specification e.g., at page 21). In particular, the Specification teaches that "[w]hen using the pharmaceutical composition in the treatment of cerebral neurodegenerative diseases, it is preferable to introduce the pharmaceutical composition to the central nervous system by an appropriate arbitrary route including an intravenous, intraspinal, **intracerebroventricular**, or intradural injection."(Id. at lines 18-23, emphasis added). Applicants submit that methods of intra-cerebroventricular injection were well know at the time of filing (See above reference to Haley TG et al) and that one skilled in the art could use these methods together with the disclosure in the Specification to make and use pharmaceutical compositions that suppresses neuronal death associated with Alzheimer's disease. This is further substantiated by the work of Tajima et al. who showed that i.c.v. injection of the claimed polypeptides suppressed neuronal death associated with Alzheimer's disease using dosages which corresponded to those disclosed in the Specification (see above). Thus using i.c.v. injection and other methods taught in the Specification, the skilled artisan would indeed know how to use the compositions of claims 13, 15, and 16 in the prevention or treatment of Alzheimer's disease. Accordingly, on this additional basis, Applicants respectfully request withdrawal of the rejection.

WRITTEN DESCRIPTION REJECTIONS UNDER 35 U.S.C. § 112, 1ST ¶

Claims 2, 4-8, 13, 15, 16, 23-27, 31-34 and 39-45 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. (See 4/13/05 Office Action, at page 5). In particular, the Examiner bases her rejection on the contention that the claims encompass a genus of polypeptides with limited or no structural similarity to the polypeptide of SEQ ID NO: 5 and the Specification "fails to describe any other proteins [besides the amino acid sequence of SEQ ID NO: 5] which lacks the amino acid sequence of SEQ ID NO:5 and has the activities of possessed by the isolated protein" (*Id.*). Each of these issues will be addressed in turn. As an initial matter, in order to expedite prosecution of the application and without acquiescing to the propriety of the Examiner's rejection, Applicants have amended claims 2, 5 and 6 to now recite that "one amino acid has been substituted, deleted, inserted, and/or added." This will result in sequence homology of greater than 95% to SEQ ID No:5. Also claims 23-26, 31-34, 39-42 and 44 have been cancelled without prejudice or disclaimer, thus mooting the rejection with respect to these claims.

Applicants respectfully disagree with the Examiner's first contention based on the Revised Interim Written Description Guidelines Training Materials. Applicants submit that instant claims 2, 5 and 6 and their respective dependant claims are analogous to the exemplary claim of Example 14, (Product by Function) of those materials. Like the exemplary claim, the genus of peptides recited in claims 2, 5 and 6 is a discrete, well-defined genus of peptides having greater than 95% homology to the disclosed species (e.g., SEQ ID No: 5 has 24 amino acids in which no more than 1 amino acid can vary). Any species of the claim can be readily envisaged. Further, as discussed herein, the function of such peptides is well defined, suppressing neuronal death associated with Alzheimer's disease. Also just like the exemplary claim, Applicants have defined an assay for determining this function, (actually, three assays: a trypan blue exclusion assay, a LDH release assay and a calcein staining assay; See the Specification e.g., at page 11, line 2 to page 12, line 1; and Examples 1-15). Just like the analysis of Example 14 of the Training materials, the "species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of

an assay which applicant provided for identifying all of the a least 95% identical variants of SEQ ID NO: .[5] ..which are capable of the specified ..activity." Therefore, "[o]ne of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus." Accordingly, Applicants respectfully request withdrawal of the rejection because in accordance with Example 14, "[t]he disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention."

Contrary to the Examiner's second basis for the rejection the Specification provides extensive disclosure of variant polypeptides of SEQ ID NO: 5 which have the activity of SEQ ID NO: 5 (e.g. suppress neuronal death associated with Alzheimer's disease). In fact, as Applicants have indicated in the response from 9/16/04, the Specification details some 22 polypeptides which suppress neuronal death associated with Alzheimer's disease. Moreover as described above, the skilled artisan can readily identify others from the finite number of species encompassed by the claims using one or more of the assays described in the Specification.

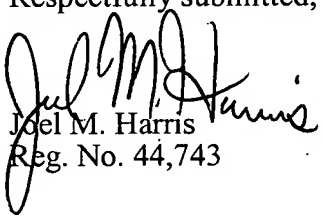
In light of the above discussion and amendments, Applicants submit that claims 2, 4-8, 13, 15,16, 27, 43 and 45 are now allowable. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments
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